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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/907,263	07/17/2001	Alison M. Bendele	A-430F	7020

7590 08/25/2003

US Patent Operations/ TJG
AMGEN, INC.
Dept. 4300, M/S 27-4-A
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

EXAMINER
O HARA, EILEEN B

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 08/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

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DATE MAILED: 07/30/2003

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Office Action Summary	Application No.	Applicant(s)	
	09/907,263	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,28-33,36,37 and 39-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,28-33,36,37 and 39-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1, 28-33, 36, 37 and 39-41 are pending in the instant application. Claims 1, 28-33, 36, 37 and 39-41 have been amended and claims 27, 34, 35 and 38 have been canceled and as requested by Applicant in Paper Number 14, filed May 7, 2003.

All claims are currently under examination.

Priority

2. Applicants' amendment to the specification to update the priority is acknowledged.

Withdrawn Rejections

3. The rejection of claim 1 under 35 USC § 102 is withdrawn in view of Applicants' amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 27-33, 36, 37 and 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobs et al., US Patent No. 5,605,690, filing date Feb. 8, 1995, further in view of Feldman et al., US. Patent No. 5,633,145 (cited by Applicant), further in view of Anderson et al., J. Clinical Invest., Vo. 97., No. 11, pages 2672-2679, June 1996, and further in

view of Hubbard et al., Arthritis & Rheumatism, "SC-58635 (CELECOXIB), a novel COX-2 selective inhibitor, is effective as a treatment for osteoarthritis (OA) in a short-term pilot study". (1996) Vol. 39, No. 9 SUPPL., p S226, for reasons of record in the previous office action, paper No. 12, at pages 3-5, and for the reasons below.

Applicants traverse the rejection and assert on page 4, lines 18-20 of the response that Jacobs et al. do not teach that the TNF binding protein may be the sTNF-RII. However, Jacobs et al. does teach that TNF antagonists, such as soluble TNFR and TNF binding proteins, bind to TNF and prevent TNF from binding to cell membrane bound TNF receptors, and such proteins may therefore be useful to suppress biological activities caused by TNF (column 1, lines 52-56), and that the TNF antagonists (binding proteins) may be either soluble TNFRI or TNFRII (column 4, lines 24-26, column 6, lines 14-21). Although Jacobs et al. do not teach combination therapy with a TNF antagonist (binding protein) and a COX-2 inhibitor, the reference teaches that combination therapy with a TNF binding protein and IL-1R was more effective in reducing the severity of arthritis than either receptor alone (Figure 4, column 13, line 56 to column 14, line 2, Example 4).

Applicants further traverse the rejection and argue that the Examiner misstated the content of Feldman et al. in that the protein of SEQ ID NO: 25 is not 100% identical to the sTNF-RII of SEQ ID NO: 4 of the instant application. This was a typographical error, and the sequence of SEQ ID NO: 25 of Feldman et al. is identical to SEQ ID NO: 2, and not SEQ ID NO: 4 of the instant application. Although Feldman et al. state at column 2, lines 10-11 that SEQ ID NO: 25 is the sequence of TNFα, this is an error the Feldman patent, and SEQ ID NO:

25 is actually the TNF-RI. Feldman et al. also teach that the TNF receptors can be used to treat diseases mediated by TNFα such as rheumatoid arthritis by their ability to bind TNFα.

Applicants also assert that contrary to the examiner's position that inhibiting two pathways involved in inflammation would be more effective than inhibiting just one pathway with a single drug, and such a combination therapy could also have synergistic effects, one could read the cited references a somewhat opposing, and that the Anderson paper notes that, although TNFα is upregulated in arthritic synovial tissue, the only drug tested in the reference had no effect on TNFα levels. Based on the Anderson paper, one could suspect that upregulation of TNFα is not a major factor in the arthritis model tested, or that TNFα might not be a good drug target because it did not have any role in prostaglandin production. Applicants also assert that one could read the cited references as directed toward alternative conditions, in that the references employ different models, and that one could speculate that from these references that TNF binding proteins and COX2 inhibitors are active against different models and perhaps ultimately different forms of arthritis, and that none of the references cited suggests combining a TNF binding protein and a COX2 inhibitor.

Applicants' arguments have been fully considered but are not deemed persuasive. Contrary to Applicant's assertions, the animal models of Anderson et al. and Jacobs et al. are the same animal model. Although Anderson et al. injected the hind footpads of Lewis rats with *M. butyricum* and Jacobs et al. injected Lewis rats with methylated bovine serum albumin in the hind knee joints, both are models of antigen-induced arthritis (AIA) that produce the same results in the rats, induction of arthritis and inflammation of the injected body part. Although the COX-2 inhibitor SC-58125 of Anderson et al. did not have an effect on TNFα levels, this is not

surprising, since many drugs that have specificity for distinct receptors or other molecules and therefore distinct physiological pathways would not necessarily affect other receptors, molecules or pathways. Inflammation and arthritis involve a number of different cytokines, receptors and other molecules, including IL-1, IL-2, TNFα, COX-2, IL-6 and prostaglandins. The cytokines IL-1 and IL-2 induce production of TNFα (Jacobs, column 13, lines 55-64), and TNFα and IL-1, as well as endotoxins and mitogens, induce production of COX-2 (Anderson et al. page 2672, second column, top paragraph), which in turn produces prostaglandins. Because COX-2 production is induced by TNFα, it would not necessarily be expected that an inhibitor of COX-2 would also affect TNFα levels or activity, but this does not mean that TNFα is not an important mediator of inflammation, since it induces COX-2 expression.

Applicants further traverse the rejection and assert that the Feldman et al., Anderson et al. and Hubbard et al. references all fail to suggest combination with a TNF inhibitor. However, the suggestion to combine a COX-2 inhibitor with a TNF inhibitor comes from Jacobs et al., which teaches that combination therapy with a TNF binding protein and another anti-inflammatory agent, IL-R, was more effective in reducing the severity of arthritis than either receptor alone. The teaching of Jacobs et al. is analogous to that of the claimed invention. IL-1 is important in TNF production, and Jacobs et al. found that inhibiting both of these cytokines was more effective in reducing the severity of arthritis than inhibiting either cytokine alone. Analogously, since it was known that TNFα induces the production of COX-2, it would have been *prima facie* to one of ordinary skill in the art to use the combination therapy of Jacobs et al., and substitute the IL-1 antagonist of Jacobs et al. with a COX-2 inhibitor, as taught by Anderson et al. and Hubbard et al. There would be a reasonable expectation of success, since Jacobs et al.

demonstrated that such a combination therapy was more effective than using one antagonist alone. Therefore, the rejection is maintained.

It is believed that all pertinent arguments have been answered.

Conclusion

5. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Patent Examiner